REMARKS

This is in response to the Final Office Action mailed March 24, 2006. Please consider this paper a petition for a three month extension of time. Please also consider this paper as a Request for Continued Examination.

Reconsideration and allowance of the subject application are respectfully requested.

Claims 1-20 and 22-46 are pending in the application. Basis for the amendment of claim 1 can be found in the present specification including at page 8, second full paragraph. Basis for new claim 46 and 48 can be found in the present specification, including at original claims 1 and 2, and page 8, second full paragraph. No new matter has been added.

The rejection of claims 1-4, 7, 10, 11, 13, 15, 22 and 27 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,858,410 (Muller) is respectfully traversed. The claimed invention is not anticipated by the Muller patent for the reasons of record and for the following reasons.

The Examiner cites the abstract and col. 20, lines 23 to 30 of the Muller patent. However, this disclosure does not anticipate the present invention for the following reasons. Dr. Muller, a named inventor of the present invention, is the same Dr. Muller named in the cited Muller patent. Thus, Dr. Muller is also knowledgeable about the teachings of his cited Muller patent.

The present invention relates to a new process. This new process is considerably different from those known in the art, including the process disclosed in the Muller patent.

Irrespective of the question of novelty of a product produced by the presently claimed process, from the complete context of the Muller patent, it is clear that with the term solvent a **water phase** was identified and not an **organic phase** because in the complete Muller patent it is referred to the importance of having cavitation and, thus, using water as dispersion medium. See column 5, lines 6-7 of Muller, which states "[t]he dispersing principle is cavitation." Cavitation requires water as

the dispersion medium. Thus, "anhydrous" or "water reduced" dispersion mediums distinguish the present process from that of the Muller patent, which requires water as the dispersion medium.

Applicants again respectfully submit that the wording in the abstract should be carefully and correctly read. The abstract describes only the solubility properties of the carrier disclosed in the Muller patent. According to the wording the carrier (or active ingredient, respectively) is "insoluble ..... in water, aqueous media and/or organic solvents" and "when introduced" into these media (i.e. the processed or finalized carrier is subsequently introduced into same) the carrier has special properties (e.g. increased saturation solubility).

Applicants respectfully submit that the abstract of the Muller patent does not describe the dispersion medium in which the carrier is prepared. There is simply no teaching in the abstract of the Muller patent regarding the dispersion medium. The dispersion medium used in the Muller patent to prepare the carrier thereof is **water**, as clearly described throughout the specification thereof. Applicants respectfully submit that the Examiner is improperly reading the abstract of the Muller patent out of context with the entire written description.

In contrast, in the present invention, an anhydrous or water-reduced medium is used as the dispersion medium. The present invention solves the problems associated with using water in a piston-gap homogenizer. It has been found that water vapor creates bubbles in a piston-gap homogenizer, which subsequently implodes (i.e. cavitation) to lead to particle diminution. This problem is avoided by the present invention. Since the Muller patent does not disclose using an anhydrous or water-reduced medium in the piston-gap homogenizer as the dispersion medium, Muller cannot anticipate the claim invention. Furthermore, by teaching to use water as the dispersion medium to produce cavitation, the Muller patent teaches in a direction opposite to the claimed invention.

Column 20, lines 35-40 of the Muller patent is claim 38. Claim 38 of the Muller patent describes a method in which as part of the process "subjecting at least one solid therapeutically active compound dispersed in a **solvent** to high pressure homogenization....". When one introduces a compound into a **solvent**, - as the

word solvent says – the compound would **dissolve**, and not be in the form of small particles any more. Thus the process of claim 38 of Muller as it is worded will not yield in nanosized particulate carrier particles, because the active ingredient would **dissolve**. The method of claim 38 of Muller yields a **solution**.

In contrast to this, according to the present invention the active ingredient is **dispersed** in a **non-solvent**, i.e. medium, which results in a **suspension**. This suspension is then subjected to high pressure homogenization to yield a nanosuspension. Thus, the Muller patent does not contain any teaching how to produce nanosized solid carriers in a non-solvent medium. For this reason alone, the Muller patent cannot anticipate the claimed invention.

Furthermore, claim 38 of the Muller patent must be read in light of its specification. The Muller patent clearly requires using water as the dispersion medium to cause cavitation, as discussed above. Thus, claim 38 must be interpreted in light of the specification of the Muller patent to require using water as a dispersion medium to provide cavitation.

In contrast, the present invention utilizes an anhydrous or water-reduced dispersion medium to avoid cavitation. For this reason alone, the Muller patent cannot anticipate the claimed invention.

In view of the differences between the Muller patent and the claimed invention, withdrawal of the Section 102 rejection is respectfully requested.

The rejection of claims 1-20 and 22-45 under 35 U.S.C. § 103 as being unpatentable over WO 98/14174 (Desai) is respectfully traversed. The claimed invention is not obvious over Desai for the reasons of record and for the following reasons.

The Examiner states that one of ordinary skill in the art would be motivated to make paclitaxel or itraconazole compositions according to methods disclosed in the cited prior art wherein the methods have been shown to provide advantages of reduced volumes and low toxicity products.

It might be assumable that one would have tried to make such small drug nanoparticles, but the essential question is: Does the disclosure of Desai lead one of ordinary skill in the art to the present invention?

The Examiner admits that in Desai, "the drug is **dissolved** in an organic solvent." See page 3 of the Office Action. In contrast, in the claimed method the matrix material is not dissolved in the anhydrous or water-reduced medium. It remains in solid particle form as a **dispersion**.

Desai teaches the preparation of a **nanoemulsion**, plus subsequent additional steps to obtain drug particles in the nano-meter range. Disruption of large **droplets of a liquid** requires "relatively" low forces (compared to disrupting solids) and appears feasible.

In contrast to this, solids are much more rigid due to their crystalline and solid character. From the Desai disclosure one would **not be motivated** to process **solid drugs** using the same process. For this reason alone, the Section 103 rejection should be withdrawn.

As discussed previously, Applicants have now found that during homgenization using a piston-gap homogenizer, water vapor can be created in the form of bubbles, which subsequently implode. The resulting implosion shock waves lead to particle diminution. However, many materials are destroyed, melted or otherwise undesirably altered by these violent shock waves. See page 3, last paragraph to page 4, first paragraph, in the present translated application.

Applicants have solved these problem by providing a far more gentler method of obtaining the same particle size without using the implosion shock waves:

1) reducing the temperature of the medium being homogenized; and/or

2) reducing or eleminating the use of water.

As discussed above, prior to the present invention, it was believed throughout the art that cavitation is the main source of diminution, as a consequence high pressure homogenization is generally described in water and especially increased effectiveness is claimed when homogenizing at higher temperatures. The reason for the increased efficiency at higher temperatures is the increased vapour pressure of water at higher temperature which provides increased cavitation. Therefore, the general teaching is the need to use water at higher temperatures to provide increased cavitation formation from water vapor to thereby provide particle diminution.

Contrary to this teaching, according to the present invention homogenization is performed in media other than water (anhydrous) or water reduced, and/or at lower temperatures to reduce or avoid cavitation from water vapor. Surprisingly, a comparable size diminution can be obtained without using destructive implosion shock waves. Contrary, to the general knowledge in the art, Applicants have found that cavitation is not the dominating diminution principle in the present invention. This is further supported by performing homogenization at lower temperatures, e.g. at 0° Celcius or below. A surprisingly similar efficiency in diminution is observed, which is contrary to the general beliefs in the art.

Desai does not disclose homogenizing solid particles and Desai does not address the problems associated with implosion shock waves from water evaporation. For these reasons, the Section 103 rejection should be withdrawn.

Desai homogenizes an emulsion (dispersed liquid in an outer liquid phase), the invention a suspension (i.e. solid dispersed in a liquid outer phase).

Desai dissolves the drug (pharmacologically active agent) in an organic phase which is subsequently dispersed in an outer phase which is subsequently passed through a high pressure homogenizer. See page 14, lines 12-24 of Desai. This process itself is a well known homogenisation process for an o/w emulsion yielding particles with a mean diameter of 200 nm to 400 nm (e.g. products Intralipid, emulsion for intravenous infusion, marketed since appr. 1960, nowadays company Baxter Healthcare, US). The knowledge that a liquid phase can be dispersed to a size below 1000 nm is known for more than have a century. Despite this knowledge, processing solid particles by the piston-gap homogenizer in water suspensions was novel, which was accepted by the US patent office by granting the Muller patent discussed above.

Especially from Desai, this conclusion cannot be drawn because Desai uses a special trick to obtain the small particles. One of ordinary skill in the art knows that the formed emulsion droplets lead to very small particles because they "shrink" due to the evaporation of the solvent in the droplets. To get even smaller particles, Desai adds water soluble solvents such as ethanol to the organic phase (page 10, lines 25-

27) which easily partitions into the water phase leading to further shrinking of the particles. That means the teaching by Desai is:

a) the drug needs to be dissolved in a liquid dispersed phase;

b) drug nanoparticles can only be achieved using volatile solvents leading to shrinking of the generated nanoemulsion droplets and subsequent formation of a solid particle;

c) especially very small particles need additionally a water soluble solvent.

From this, i.e., from a disclosed emulsion patent with high pressure homogenization, it cannot be concluded that also hard crystalline particles can be processed to nanoparticles (<1000 nm) using this method. As already pointed out, the required dispersion forces for a liquid are dimensions lower than for a crystalline material.

Production of a powder from a suspension by removal of the outer phase or sterilization by filtration described by Desai are not special features, these are common techniques which can be combined with any novel, innovative particulate system as further processing steps and represent no prior special art with regard to the present invention.

On page 3, last line and page 4, 1st line, of the Office Action, the Examiner states that Deasi decribes the effect of solvents how to make small particles. However, in case of Deasi the solvent is:

a) the dissolution medium for the drug,

b) the inner phase of the emulsion system,

b) it needs to be evaporated to finally yield the small particles (Fig. 1).

In the present invention, the solvent

a) does not dissolve the drug, i.e. the prerequisite of the invention is that the solvent does not dissolve the drug,

b) is the outer phase of the dispersion to be homogenized, not the inner phase,

c) does not need to be evaporated to obtain the particle.

That means the only common thing between Desai and the present invention is that a solvent is used, but in a completely different manner. The teaching by Desai rather directs into a completely different direction, that means to the processing of solutions.

The Examiner states on page 4, 2nd paragraph of the pending Office Action, that Desai disclosed advantages of small particles and everybody would be motivated to make them.

Firstly, it is correct, that everybody wants to make them, which is secondly known long before Desai and textbook know-ledge since decades in Pharmaceutical Technology and Biopharmaceutics. However, the obvious desire to have something does not teach how to make it. The teaching for the present invention is not disclosed in Desai. An expressed desire is not prior art to making the desired something.

Claim 1 of Desai describes a completely different process, and different processing steps of dissolving the active in the solvent etc. It is not identical with claim 1 of the present invention.

Please find enclosed also hand-drawn Fig.s (1 to 3) showing again the differences between Desai and the claimed invention.

In view of the many differences between Desai and the claimed invention, withdrawal of the Section 103 rejection is respectfully requested.

The rejection of claims 44 and 45 under 35 U.S.C. § 103 over Desai in view of U.S. Patent No. 5,104,674 (Chen) is respectfully traversed. The claimed invention is not obvious over Desai in view of Chen for the same reasons claim 1 is not obvious over Desai and Chen, the for the following reasons.

Chen recites in claim 1:

"1. A method for producing a microfragmented anisotropic xanthan/protein complex dispersion comprising the steps of forming an aqueous suspension of molecularly intimately complexed xanthan/protein fibers comprising at least 7 weight percent of xanthan gum based on the total solids weight of said fibers, conducting said **aqueous** fiber suspension through a zone of high shear to fragment the fibers under sufficient conditions of shear and duration

> to reduce substantially all of said fibers to xanthan/protein complex microfragments having a maximum dimension of less than about 15 microns."

This means that Chen is using water as dispersion medium and obtains particles in the micrometer range. The aqueous phase contains e.g. polysaccharides, no mixtures of water with other water miscible liquids are described. Thus, the combination of Desai and Chen uses water. For this reason alone, the Section 103 rejection should be withdrawn.

Chen is using high speed stirrers, e.g. as said on page 12. The high shear zone should best have a shear rate of at least about 37,000 inverse seconds, with a turbulent energy dissipation rate sufficient to raise the temperature of the suspension at least about 5° C. through viscous dissipation of input energy to heat.

Page 16 of Chen describes a Gaulin machine, but it states that only particles in the low micrometer range can be obtained, no teaching about nanofragments:

> Effective results have been achieved by using a CD150 or a MC15 cell disruptor using a knife edge homogenization element within a closely surrounding impact ring (A.P.Z. Gaulin Corp., Boston, Mass.) at an inlet pressure of at least about 3000 psig and preferably at least 10,000 psig to obtain microfragments smaller than fifteen microns preferably smaller than 5 microns in maximum dimension.

In example 1 Chen uses a jet stream homogenizer, that means high pressure honmogenization is clearly covered (at least jet-stream): "Microfluidizer model 110Y sold by Biotechnology Development Corporation of...."

Also claim 26 of Chen reads:

> 26. A microfragmented syneresed ionic polysaccharide/protein complex dispersion in accordance with claim 24 comprising microfragments having a mean maximum dimension in the range of from about 2 to about 10 microns.

In contrast, present claim 46 recites particles "5.6 µm or less," which are not included in Chen's particle range of 2 to 10 microns. For this reason alone, the Section 103 rejection should be withdrawn.

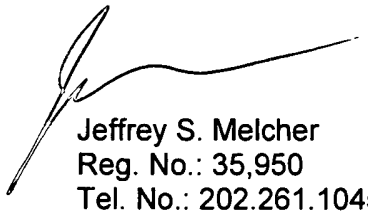
In view of the many differences between the claimed invention and the theoretical combination of Desai and Chen, withdrawal of the Section 103 rejection

is respectfully requested.

In view of all of the rejections of record having been addressed, Applicants submit that the claimed invention is in condition for allowance and Notice to that effect is respectfully requested.

Respectfully submitted,

Manelli Denison & Selter, PLLC

By 

Jeffrey S. Melcher
Reg. No.: 35,950
Tel. No.: 202.261.1045
Fax. No.: 202.887.0336

Customer No. 20736